

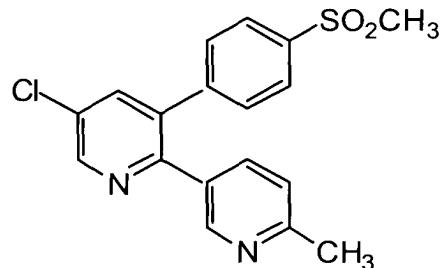
TITLE

POLYMORPHIC, AMORPHOUS AND HYDRATED FORMS OF

5 5-CHLORO-3-(4-METHANESULFONYLPHENYL)-6'-METHYL-[2,3']BIPYRIDINYL

BACKGROUND OF THE INVENTION

10 The present invention relates to polymorphic, amorphous and hydrated forms of the title compound which has the chemical structure shown below:



15 Compound A

The compound is a potent and selective cyclooxygenase-2 (COX-2) inhibitor, useful primarily in the treatment of inflammation, pain and fever as well as other COX-2 mediated diseases, such as described in PCT Publication Nos. WO96/10012 and WO96/16934. Compound A is described in US Patent No. 5,861,419 granted on January 19, 1999 (Example 23) incorporated by reference in its entirety.

20 Bipyridyl compounds generally are highly crystalline, poorly water soluble and hydrophobic, resulting in difficulties in the preparation of pharmaceutical formulations and problems associated with bioavailability. Accordingly, efforts were made to discover other forms of Compound A and to investigate the properties thereof. There were discovered three additional polymorphic forms, an amorphous form and two hydrates.

25 30 SUMMARY OF THE INVENTION

Polymorphic forms of Compound A, for purposes of this invention, are identified as Form I (onset of melting, m.p. 134-136°C, peak m.p. 138°C), Form II (onset of melting, m.p. ~131°C, peak m.p. 133°C), Form III (onset of melting, m.p. ~133°C, peak m.p. 135°C) and Form IV (onset of melting, m.p. ~134°C, peak m.p. 136°C). Forms I through IV are anhydrous. An amorphous form and two hydrates have also been identified.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention is described in connection with the appended drawings in which:

Fig. 1 is the X-ray powder diffraction (XRPD) pattern of Form I;
Fig. 2 is the XRPD pattern of Form II;
Fig. 3 is the XRPD pattern of Form III;
Fig. 4 is the XRPD pattern of Form IV;
Fig. 5 is the XRPD pattern of the hemihydrate;
Fig. 6 is the XRPD pattern of the sesquihydrate;
Fig. 7 is a thermogravimetric (TG) scan of the hemihydrate, and
Fig. 8 is a TG scan of the sesquihydrate.

DETAILED DESCRIPTION

Polymorphic forms of Compound A, for purposes of this invention, are identified as Form I (onset of melting, m.p. 134-136°C, peak m.p. 138°C), Form II (onset of melting, m.p. ~131°C, peak m.p. 133°C), Form III (onset of melting, m.p. ~133°C, peak m.p. 135°C) and Form IV (onset of melting, m.p. ~134°C, peak m.p. 136°C). Forms I through IV are anhydrous. An amorphous form and two hydrates have also been identified.

The polymorphs of the present invention are synthesized in accordance with the following examples which are illustrative.

PREPARATIVE EXAMPLE 1

The starting material compound A is made in accordance with Example 23 of U. S. Pat. No. 5,861,419 granted on January 19, 1999.

EXAMPLE 1 FORM II

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Form II is obtained by crystallizing compound A obtained in accordance with Preparative Example 1 from ethyl acetate.

Differential Scanning Calorimetry showed an extrapolated onset of melting at $131\pm1^{\circ}\text{C}$, and a peak melting point of $132.5\pm0.1^{\circ}\text{C}$.

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EXAMPLE 2
FORM I

Form I was obtained by recrystallizing Form II obtained as described in Example 1 from a solvent mixture of isopropanol/hexane.

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EXAMPLE 3
FORM IV

Form IV appeared spontaneously in batches of compound A prepared as in Preparative Example 1.

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Form IV is alternatively prepared by contacting Form I as described in Example 2 with an organic solvent, e.g., toluene and heptane, and then recrystallizing at a temperature less than 45°C , such as about 15°C .

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Form IV is also alternatively prepared by dissolving Form II in an organic solvent, such as toluene and heptane, and then recrystallizing at a temperature less than 45°C , such as about 15°C .

EXAMPLE 4
FORM III

Form III was prepared by stirring Form IV from Example 3 in water for 1 day, and then dehydrating at 90°C in vacuo until Form III is present. The melting temperature onset was ca. 133°C with an enthalpy of fusion of approximately 24 kJ/mol . The peak melting temperature was 135°C .

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Alternatively, using the hemihydrate of Example 5, conducting a temperature XRPD of the hemihydrate at 130°C resulted in the production of Form III.

EXAMPLE 5
HEMIHYDRATE

The hemihydrate form of compound A is produced by stirring Form IV obtained in accordance with Example 3 in water for at least 1 day.

- XRPD analysis of the solid produced a diffractogram identical to previous hemihydrate samples obtained for Form II. Thermogravimetry confirmed that Form IV had converted to the hemihydrate form, exhibiting a sharp weight loss of 2.45% on heating, which corresponds to a mole ratio of water to drug of
- 5 0.50%.

EXAMPLE 6
SESQUIHYDRATE

The sesquihydrate of compound A is obtained by combining

- 10 Form I in accordance with Example 2 and water (approximately 1.5 mol/mol compound).

EXAMPLE 7
AMORPHOUS

- 15 The amorphous form of compound A is obtained by heating any polymorph to above its melting temperature (for example to 145°C) under nitrogen, followed by quench cooling to room temperature under a dry atmosphere.

20 CHARACTERIZATION OF POLYMORPHS

The polymorphic forms of compound A are characterized using the following procedures.

X-Ray Powder Diffraction Pattern Analysis

5 Polymorph I is crystalline by XRPD using a Scintag XDS-2000, Si(Li) Peltier-cooled solid state detector using a Cu K alpha source at 45 kV and 40 mA, and divergent beam (2 mm and 4 mm) and receiving beam slits (0.5 mm and 0.2 mm). Peak positions were calibrated using a standard silicon disk (97.5% pure).

Temperature XRPD studies were carried out under nitrogen, using a gold-plated copper stage with a Beryllium window on the cover. A Micristar temperature controller monitored and controlled the temperatures.

10 Temperature XRPD studies demonstrated that the compound did not undergo any transitions prior to melting, which was complete at 140°C, and that there was no conversion to a different polymorphic form. Similar results were obtained for Form II. The material remained amorphous and did not recrystallize.

15 Table 1 below lists the XRPD peak locations for Forms I, II, III and IV.

TABLE 1

X-ray Crystalline Reflections in °2 theta That Are Characteristic of Polymorphs I, II, III and IV using Cu K alpha

Form I	Form II	Form III	Form IV
7.1	5.6		8.7
9.7	9.4	10.5	
11.8	10.7	16.1	
15.5	17.6		15.2
20.1			17.1
			19.5
22.7		22.4	21.7
24.1			23.5
			23.6

XRPD patterns for Forms I-IV are shown in Figures 1-4.

XRPD patterns for the two hydrate forms are shown in Figures 5 and 6.

25 Differential Scanning Calorimetry (DSC)

The extrapolated melting temperature onset of Form I was $134.0 \pm 0.6^\circ\text{C}$ with an enthalpy of fusion of $27.2 \pm 0.9 \text{ kJ/mol}$ at 10 deg/min under nitrogen in crimped aluminum pans (Fig. 1). **The peak melting temperature was 138°C .**

5 When measured using a TA Instruments DSC2910 instrument, at 10°C/min under a nitrogen atmosphere in an open aluminum pan, the onset of melting was 136°C and the peak melting temperature was as described above. There were no significant changes with DSC scanning rate other than the expected shift in peak temperature.

10 DSC thermal behaviour of Form I in crimped sample pans under nitrogen (60 mL/min) was measured using a Seiko robotic DSC (RDC-220) at $2, 10$ and 20 deg/min . The DSC was calibrated for temperature and heat flow with gallium, indium and tin.

15 The melting temperature onset and enthalpy of fusion of Form I were slightly higher than those observed for Form II. These polymorphic forms do not recrystallize upon cooling from the melt nor do they recrystallize on reheating. The glass transition temperature of the amorphous form (mid-point, 10K/min , crimped aluminum pan) is 55°C .

20 Table 2 provides a comparison of the extrapolated melting temperature onset, T_o , and the enthalpy of fusion, ΔH , for Forms I, II, III and IV.

TABLE 2
Extrapolated melting temperature onset, T_o , and Enthalpy of Fusion obtained
by DSC at 10K/min in crimped pans under nitrogen

Polymorphic form	T_o ($^\circ\text{C}$)	Enthalpy of fusion, kJ/mol
Form I	134.0 ± 0.6	27.2 ± 0.9
Form II	131 ± 1	25.8 ± 0.2
Form III	133	22.7
Form IV	134.0 ± 0.1	27.9 ± 0.2

30 The DSC thermogram for Form IV, obtained at a scanning rate of 10°C/min under nitrogen in crimped aluminum pans, consisted of a single symmetrical endotherm with a mean onset melting point of $134.0 \pm 0.1^\circ\text{C}$ and a heat of fusion of 27.9 kJ/mol . A scanning rate of 2°C/min confirmed that the

observed endotherm was due to a single endothermic transition. The enthalpy of fusion of the different polymorphs are also similar.

Forms I and IV have similar solubilities. Form IV is slightly less soluble and slightly more stable at temperatures below 45°C. Forms I and IV

5 are enantiotropic with Form IV converting to Form I at temperatures greater than 45°C when in contact with organic solvents.